Express Mail Label No.: EV463103254US
Date of Deposit: October 12, 2005

Attorney Docket No. 26448-506

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

APPLICANTS : Egan et al.
SERIAL NUMBER : 10/038,112 EXAMINER : Cybille Delacroix-Muirheid
FILING DATE : December 31, 2001 ART UNIT : 1614
FOR : METHODS FOR TREATING GLAUCOMA IC

Mail Stop RCE
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF HOWARD B. HAIMES UNDER 37 C.F.R. §1.132

I, Howard B. Haimes, of 114 Woodland Street, Natick, MA, declare and state that:

1. I received Ph.D. degree in Biochemical Cytology from Sue Golding Graduate Division of the Albert Einstein College of Medicine, Yeshiva University, Bronx, NY and a M.S. in Biochemical Cytology from Sue Golding Graduate Division of the Albert Einstein College of Medicine, Yeshiva University, Bronx, NY and an M.S. degree in Biology from Long Island University, Brooklyn, NY and a B.S degree in Biology from Union College, Schenectady, NY .

2. I am presently employed by Alteon Inc., 6 Campus Drive, Parsippany, NJ 07054, the assignee of the above-referenced patent application. I have been employed by Alteon Inc. for over one year.

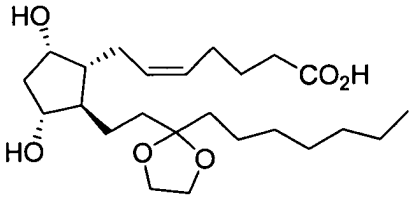
3. I have reviewed the Final Office Action dated January 11, 2005 and the Advisory Action dated May 23, 2005. I understand that claims 1, 2, 4, 7, 8, 9, 11 and 13-17 unpatentable over U.S. Patent 5,853,703 to Cerami ("Cerami") in view EP 0 458 589 A1 to Kabushiki ("Kabushiki").

4. I have reviewed the present application in conjunction with the Cerami and Kabushiki references.

5. I disagree with the Examiner's assertion it would be obvious to combine the thiazolium compounds of Cerami with the cholinergic agents of Kabushiki to decrease intraocular pressure or improve ocular accommodation with a reasonable expectation of success have reading the entirety of the Kabushiki reference.

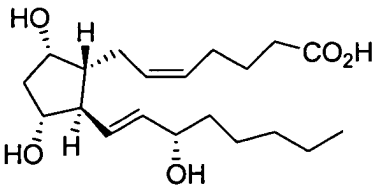
6. Kabushiki teaches that only **certain** prostaglandins (13,14-dihydro-15-ketoprostaglandins) in combination with cholinergic agents are able to treat ocular hypertension. Other prostaglandins ($PGF_2\alpha$) when combined with cholinergic agents **lose** their ocular pressure lowering activity (**Emphasis Added**). Although both classes of prostaglandins (13,14-dihydro-15-ketoprostaglandins and $PGF_2\alpha$) have very similar structures (*infra*) and are known in the art to treat ocular hypertension alone as a monotherapy, Kabushiki teaches that only one these classes (13,14-dihydro-15-ketoprostaglandins) is able to treat ocular hypertension when in combination with a cholinergic agent.

Compare:



13,14-dihydro-15-ketoprostaglandin

with



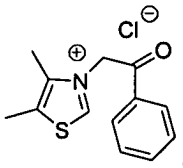
PGF2a

After reading Kabushiki, as a whole, in combination with Cerami, although members of the prostaglandin family are similar in structure (all contain 20 carbon atoms, including a non-planar 5-membered aliphatic ring), their functional activity is divergent and unpredictable when combined with a cholinergic agent, such as pilocarpine.

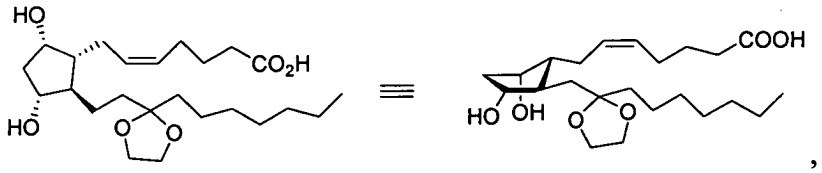
7. I assert that one of ordinary skill in the art reading Cerami in combination with Kabushiki, as a whole, would readily recognize there is no reasonable expectation of success in combining any prostaglandin with any cholinergic agent because the functional activity of the combination is unpredictable. I further assert that the skilled artisan would readily recognize that if there is such functional unpredictability amongst prostaglandin family members when in combination with a cholinergic agent, there is no reasonable expectation of success in

combining the thiazolium compounds of Cerami with the cholinergic agents of Kabushiki to reach the present invention

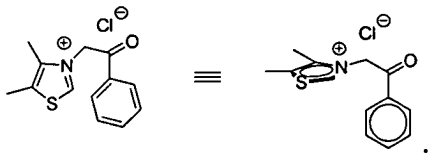
8. Thiazoliums are aromatic 5-membered rings, which have the special property of being flat, planar molecules. The thiazolium compounds of the instant invention are heteroaromatic, charged molecules which inhibit the formation of (or reverse) pre-formed advanced glycosylation of proteins (advanced glycosylation end products, AGEs). One example includes 3-(2-phenyl-2-oxoethyl)-4,5-dimethylthiazolium chloride:



On the other hand, prostaglandins are a well known group of naturally occurring lipid molecules which are derived from fatty acids and present in virtually all tissues and organs. Prostaglandins act on a variety of cells such as vascular smooth muscle cells causing constriction or dilation, on platelets causing aggregation or disaggregation and on spinal neurons causing pain. Prostaglandins are most commonly known in the art to cause muscular constriction and mediate inflammation. Every prostaglandin contains 20 carbon atoms, including a 5-membered aliphatic carbon ring. The 5-ring structure of prostaglandins is, however, not planar. For example, the prostaglandin, 13,14-dihydro-15-ketoprostaglandin, of Kabushiki is thought to have the following structure:



whereas the 5-membered ring in the thiazolium compounds of the invention (exemplified below by 3-(2-phenyl-2-oxoethyl)-4,5-dimethyl-thiazolium chloride) has a flat, planar structure:



9. Since prostaglandins and thiazolium compounds are structurally and functionally distinct, and because the teachings of Kabushiki, as a whole, show that the combination of any prostaglandins with any cholinergic agents is not reasonably expected to be effective in treating ocular hypertension, I assert that the skilled artisan would have no reasonable expectation of success combining the methods of using the thiazolium compounds of Cerami with the cholinergic compounds used in the methods of Kabushiki to reach the present invention.

10. The eye constantly produces aqueous humor, the clear fluid that fills the anterior chamber (the space between the cornea and iris). The aqueous humor filters out of the anterior chamber through a complex drainage system. The delicate balance between the production and drainage of aqueous humor determines the intraocular pressure. Normal human intraocular pressure ranges between 8mm and 21mm Hg. Increased intraocular pressure indicates a problem with the amount of aqueous humor in the eye: either the eye is producing too much, or it's not draining properly. High intraocular pressure is a major risk factor for glaucoma. Glaucoma is an eye disorder that causes progressive and irreversible optic nerve damage and vision loss.

    Although not everyone with intraocular pressure above 20mm Hg develops glaucoma, someone with the pressure over 20mm Hg is more likely to develop glaucoma than someone with a lower pressure. Also, there are some people who have an intraocular pressure below 20mm Hg who develop glaucoma, this is called normal tension glaucoma.

    Depending on the type of glaucoma, various symptoms may be experienced. There is gradual loss of peripheral vision and night vision. Blurred vision and colored rings around lights accompany these symptoms. If intraocular pressure remains high, tunnel vision can develop.

    Glaucoma Risk factors include age, race (African-Americans and persons of Japanese decent have a higher incidence of glaucoma), sex (females are high risk), family history and medical disorders (*e.g.*, presence of hyperopia or farsightedness, diabetes or previous eye injury). Although glaucoma cannot be cured, in most cases it can be successfully controlled. Glaucoma treatment entails decreasing aqueous humor production, increasing fluid drainage

or a combination of the two, thereby decreasing intraocular pressure. Intraocular pressure treatment may be in the form of medication (*e.g.*, eye drops containing beta-blockers or alpha-2 agonists), laser therapy or surgery (*e.g.*, trabeculoplasty, trabeculectomy).

11. Diabetic retinopathy is a disorder of the retinal blood vessels resulting from diabetes. Everyone who has diabetes is at risk for developing diabetic retinopathy, but not all diabetics do develop it. The incidence of diabetic retinopathy increases with the duration of diabetes. About 60% of patients having diabetes for 15 years or more will have some blood vessel damage in their eyes and a percentage of these are at risk of developing blindness. Patients with diabetic retinopathy are also at a greater risk of developing retinal tears and detachment.

In diabetic retinopathy, the small blood vessels that are in the retina are damaged and become leaky. New blood vessels can also grow in the back of the eye. These new vessels are abnormal and bleed easily, sometimes filing the back of the eye with blood. This causes the retina to swell and form deposits. The affect of diabetic retinopathy on vision varies widely, depending on the stage of the disease. Some common symptoms include blurred vision, floaters and flashes and sudden vision loss. Risk factors for diabetic retinopathy include high blood glucose, poor diet and lack of exercise.

Diabetic retinopathy is treated in many ways, depending on the stage of the disease and the specific problem that requires attention. The preferred method of treatment is laser photocoagulation to seal off leaking blood vessels and destroy new growth or in more extensive cases, vitrectomy. Many patients control their diabetes with diet and medication to delay or prevent the development of diabetic retinopathy and other complications.

Although diabetes and diabetic retinopathy are risk factors for increased intraocular pressure and glaucoma, not all diabetics or people suffering from diabetic retinopathy develop increased intraocular pressure or glaucoma. In fact, while most diabetics develop diabetic retinopathy over time, the same cannot be said for intraocular pressure and/or glaucoma. Specifically, the instant specification teaches that primary open angle glaucoma (the predominant form of glaucoma) occurs in approximately 4% of diabetics compared to 1.8% of the general population. *See*, page 1, lines 18-32.

12. Cataracts are a disorder characterized by a clouding of the eye's natural lens, which lies behind the iris and the pupil. The lens is mostly made of water and protein. The protein is arranged in a precise way that keeps the lens clear and lets light pass through it. But as people age, some of the protein may clump together and start to cloud a small area of the lens. This is a cataract, and over time, it may grow larger and cloud more of the lens, making it harder to see. Cataracts are classified as one of three types: nuclear, cortical or subcapsular. The type of cataract you have will affect exactly which symptoms you experience and how soon they will occur.

    In general, it is not clear why the eye's lens changes over time, forming cataracts; however, risk factors include exposure to ultraviolet light or other forms of radiation, cigarette smoke, air pollution, heavy alcohol consumption, diet high in salt, diabetes and the use of steroids, diuretics and major tranquilizers

    When symptoms begin to appear, vision may be improved temporarily using new glasses, strong bifocals, magnification, appropriate lighting or other visual aids. However, cataract surgery, which involves the replacement of the clouded lens with a clear, plastic intraocular lens, is recommended for most cataract sufferers and is very successful in restoring vision.

    Cataracts are a separate disorder, unrelated to glaucoma or increase intraocular pressure. The only relation between cataracts and glaucoma or increase intraocular pressure is that these disorders share diabetes as one risk factor.

13. I assert that one of ordinary skill in the art would readily recognize that the etiology, symptoms and treatment of glaucoma/increased intraocular pressure is quite different from that of diabetic retinopathy or cataracts and would further recognize that while diabetics are twice as likely to develop glaucoma as compared to the general population, glaucoma/increased intraocular pressure is not a natural consequence that necessarily flows from diabetes, diabetic retinopathy or cataracts.

14. I further declare that all statements made herein of our own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under 18 U.S.C. § 1001 and that willful false statements may jeopardize the validity of this application and any patent issuing therefrom.

Howard B. Haimes

Signed at Parsippany, NJ

this 12th day of October, 2005

TRA 2071126v1